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REVIEW

Origin of oligodendrocytes in mammalian forebrains: a revised perspective

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Abstract Oligodendrocyte precursor cells (OPCs) appear in the late embryonic brain, mature into oligodendrocytes (OLs), and form myelin in the postnatal brain. It has been proposed that early born OPCs derived from the ventral forebrain are eliminated postnatally and late-born OLs predominate in the adult mouse cortex. However, the temporal and regional niche for cortical OL generation, which persists throughout life in adult mammals, remains to be determined. Our recent study provides new insight into self-renewing and multipotent neural stem cells (NSCs). Our results, together with previous studies, suggest that NSCs at the dorsoventral boundary are uniquely specialized to produce myelin-forming OLs in the cortex during a restricted temporal window. These findings may help identify transcription factors or gene expression patterns which confer neural precursors with the characteristic ability of dorsoventral boundary NSCs to differentiate into OLs, and facilitate the development of new strategies for regenerative medicine of the damaged brain.

Keywords Cortical oligodendrocyte · Dorsoventral boundary · Neural stem cells · Wnts · FGF

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> …as the name "interfascicular glia" indicates only the principal feature of its constitutive elements, we have adopted the term "oligodendroglia"…Unfortunately, we have not been able to observe the very first stages of genesis of the oligodendroglia… by Pío Del Río-Hortega [1]

Introduction

Myelination of axons by mature cortical oligodendrocytes (OLs) starts during late embryonic stages and persists long into adulthood in the mammalian brain [2]. This led to the notion that cortical OLs are "generated" in the postnatal brain for a fairly extended period—but, "generated" from what? All OLs are considered to be progeny of neural stem cells (NSCs), which are present not only in embryonic brains but also in specific neurogenic regions of the adult brain, and produce new neurons in the olfactory bulb and dentate gyrus of the hippocampus [3, 4]. NSCs proliferate during early embryonic stages, produce neurons during middle embryonic stages, then generate OLs and astrocytes during late embryonic to postnatal stages (Fig. 1). Oligodendrocyte precursor cells (OPCs) represent an intermediate stage in oligodendrogenesis but also persist in the adult cortex as $Olig2^{+}$/$NG2^{+}$ cells [5, 6]. OPCs vigorously proliferate just before terminal differentiation into mature OLs [7]; this makes birthdating studies of OLs extremely difficult because common labels using nucleotide analogues, such as BrdU, would be diluted to below detection limits. Therefore, the temporal window in which OL-lineage cells are segregated from self-renewing and multipotent NSCs remains elusive.

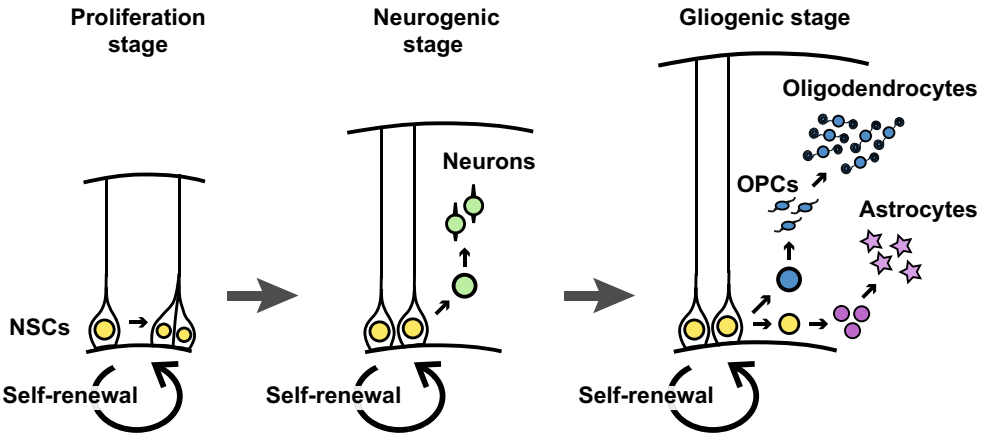

Fig. 1 Neural stem cell (NSC) proliferation and differentiation in the embryonic mouse brain. Neural stem cells (shown in *yellow*), or radial glial cells, produce neurons (*green*) in the middle embryonic stage, and then oligodendrocytes (*blue*) and astrocytes (*purple*) in the late embryonic stage

Temporal window of oligodendrocyte generation

Lineage tracing system

Self-renewing NSCs in the developing brain produce multipotent, non-self-renewing neural progenitor cells (NPCs). Once NSCs exit the self-renewing cycle, differentiation appears uni-directional into lineage-committed progeny [8, 9]. To examine when NSCs exit the self-renewing stem cell population and begin to differentiate into OPCs, we established a system to separately label the self-renewing NSC population and non-self-renewing NPC/OPC population at various time points [10]. We utilized a Cre-LoxP system in which Cre-Estrogen Receptor (ER) fusion protein-expressing cells can be permanently labeled at specific time points by injection with 4-hydroxytamoxifen (4-OHT) to induce recombination and expression of a reporter gene, such as GFP in the Z/EG reporter mouse line. In *Nestin*-CreER;Z/EG double transgenic mice, *CreER* expression is driven by the *Nestin* promoter/enhancer to reflect the endogenous *Nestin* gene expression pattern that is restricted to the VZ/SVZ, where self-renewing NSCs reside. If administration of 4-OHT labels self-renewing neural stem cells, labeled cells should remain in the VZ/SVZ during later developmental stages and yield GFP^+ neurospheres in in vitro colony-forming NSC cultures (a neurosphere assay). Indeed, 3 days after 4-OHT administration to E11.5 *Nestin*-CreER;Z/EG embryos, GFP^+ cells were found in the VZ/SVZ, some of which formed GFP^+ neurospheres in the neurosphere assay (Fig. 2a).

Olig2, which is considered an OL-lineage cell marker, is expressed in the VZ/SVZ of embryonic brains in a pattern very similar to that of *Nestin*. In addition to OLs, *Olig2*-lineage cells differentiate into neurons and astrocytes [10–13], suggesting that it is expressed in multipotent neural stem/progenitor cells (or collectively, neural precursor cells). However, *Olig2*-lineage cells did not remain in the VZ/SVZ but migrated out to differentiate and never formed GFP^+ neurospheres (Fig. 2a), in sharp contrast to *Nestin*-lineage cells. This difference in *Nestin*- and *Olig2*-lineage cells makes it possible to differentially label multipotent and self-renewing NSCs and their non-self-renewing and OL-lineage progeny (Fig. 2b).

Restricted period of OL lineage cell differentiation

We administered 4-OHT to *Nestin*-CreER;Z/EG and $Olig2^{CreER}$;Z/EG embryos at E12.5, E16.5, or P10 and examined the presence or absence of GFP^+ cells in the cortex at P30 (Fig. 2c). GFP^+ cortical OLs were observed in *Nestin*-CreER mice treated with 4-OHT at E12.5 or E16.5 but not at P10, demonstrating that the generation of OL-lineage cells from the NSC population has ceased by P10. On the other hand, while there are many GFP^+ OLs in the cortex of $Olig2^{CreER}$ mice treated with 4-OHT at E16.5 or P10, no GFP^+ cortical OLs were detected in those treated at E12.5, suggesting that NPCs, which are fated to become cortical OLs in the adult brain, have yet to be generated from NSCs at E12.5. These results suggest that neural progenitor cells, which subsequently differentiate into cortical OLs in the adult brain, are derived from self-renewing NSCs during a period just prior to E16.5 through P10.

Oligodendrocyte generating niche in the developing brain

Patterning of the central nervous system

In the developing central nervous system (CNS), morphogens such as bone morphogenetic proteins (BMPs), Wnts, sonic hedgehog (Shh), and fibroblast growth factors (FGFs) form concentration gradients along the dorsoventral and anteroposterior axes, and contribute to

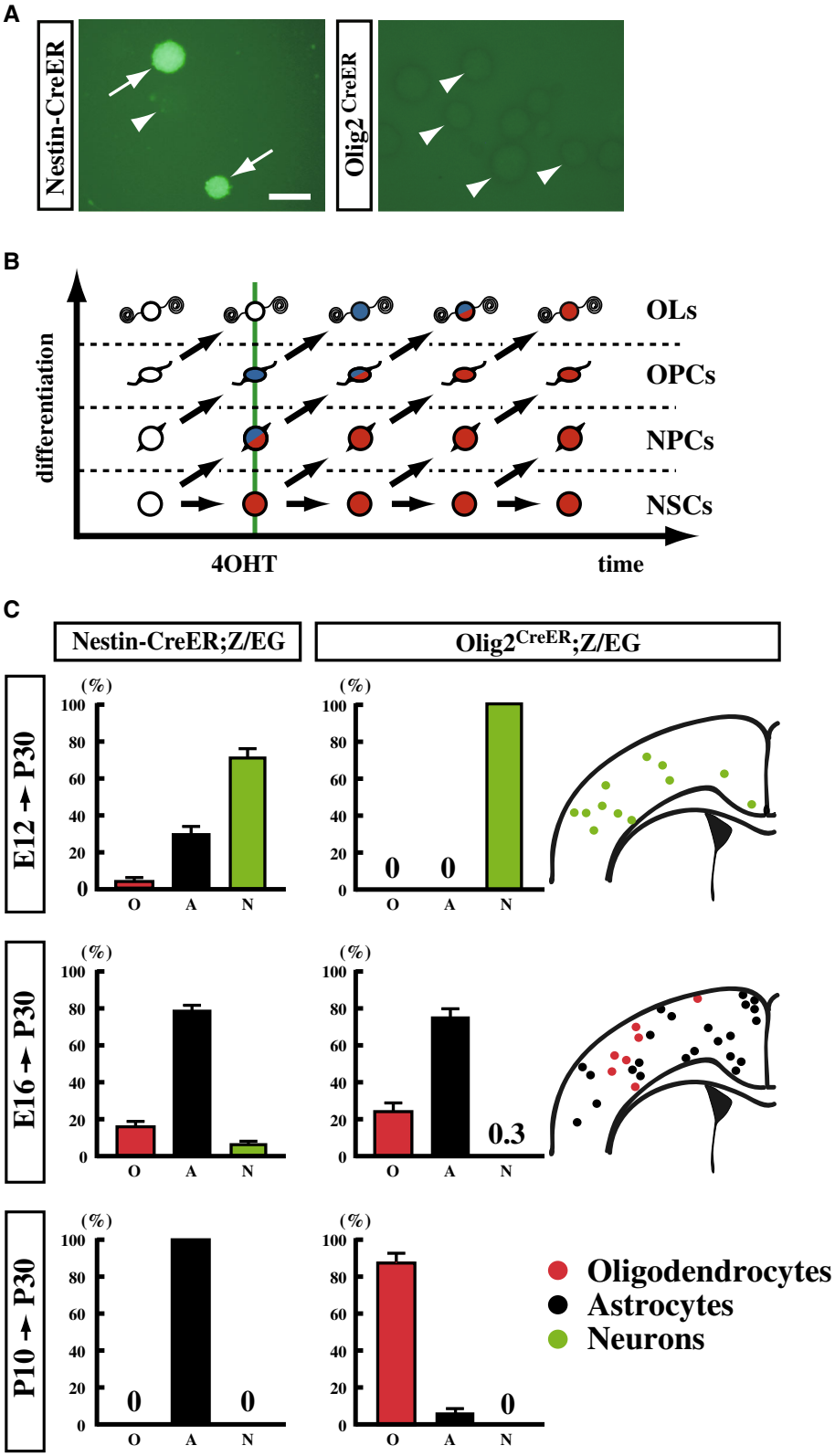

Fig. 2 Lineage tracing using Cre recombinase transgenic/knock-in mice. **a** *Nestin*-CreER;Z/EG and *Olig2*^{CreER};Z/EG embryos were labeled by injection of 2 mg 4-hydroxytamoxifen (4OHT) intraperitoneally into the dam at E11.5, then cells from the germinal zone of the ganglionic eminence were used in a colony-forming neurosphere assay at E14.5. Neurospheres with or without GFP expression are indicated by *arrows* or *arrowheads*, respectively. *Scale bars* 200 μm. **b** Schematic diagram of *Nestin*- and *Olig2*-lineage progeny (cells shown in *red* and *blue*, respectively) of neural precursor cells labeled by injection with 4OHT (shown as a *vertical green line*). **c** *Nestin*-CreER;Z/EG and *Olig2*^{CreER};Z/EG mice were labeled at the indicated times and brains were analyzed at P30. GFP^{+} cells in the cortex were classified as oligodendrocytes (O), astrocytes (A), or neurons (N) based on morphology, and the number of cells from each type were counted (modified from Naruse et al. [10])

the developmental patterning and regional differentiation of NSCs [14, 15] (Fig. 3). BMPs and Wnts are secreted from the roof plate of the spinal cord and the cortical hem of the telencephalon, and contribute to dorsal patterning [15–19]. Conversely, Shh is secreted from the floor plate and notochord of the spinal cord, and from the ventral

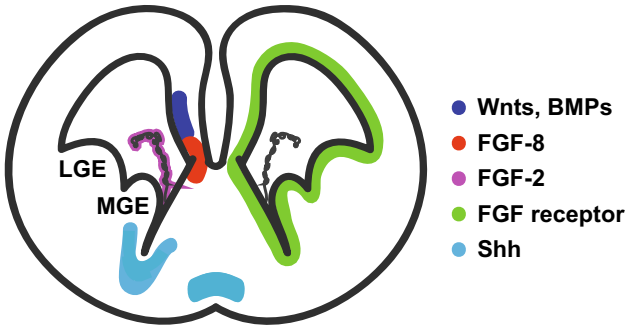

Fig. 3 Distribution of morphogens, which may influence oligodendrogenesis in the embryonic brain, and FGF receptors is shown in a scheme of the coronal section of E14.5 mouse brain. LGE and MGE mean lateral and medial ganglionic eminence, respectively

regions of the telencephalon [20, 21], leading to the establishment of ventral patterning [22–25]. While NSCs are regionally specified along the dorsoventral and anteroposterior axes [26, 27], neurons and astrocytes are produced from most, if not all, regions of the VZ/SVZ throughout the entire CNS. In contrast, oligodendrocyte generation takes place in a few restricted regions, although the specific origins of OLs in the CNS have been controversial for years. Recent studies, including ours, have provided a new perspective on this issue; in this section, the current views on the source of OLs in both the spinal cord and forebrain will be discussed.

Traditional perspectives on oligodendrocyte generation—spinal cord

The developmental origin of OLs has been extensively investigated in the spinal cord through analysis of several knockout mouse lines. Around E12, OL-lineage cells expressing platelet-derived growth factor alpha-receptor (PDGFRα), an established marker for OPCs, are derived from the motor neuron progenitor (pMN) domain (Fig. 4a). The pMN domain harbors specialized neural precursor cells, which first give rise to motoneurons, then switch their fate to produce OPCs [28]. Shh is secreted from the floor plate and notochord, and is indispensable for ventral patterning of the developing spinal cord [29]. Mouse embryos deficient for Shh or both Nkx6.1 and Nkx6.2, homeodomain transcription factors expressed under the influence of Shh, completely lack $Olig2^+$ OPCs in the early stage spinal cord [30, 31]. Olig2, a basic helix-loop-helix (bHLH) transcription factor, is expressed in NPCs of the pMN domain and plays an essential role in the development of motoneurons and OPCs [32–34]. This role was demonstrated in studies of *Olig2*-deficient mice, which were found to be devoid of motoneurons and OPCs in the spinal cord and die shortly after birth [35, 36]. It was recently reported that phosphorylation of the Olig2 bHLH

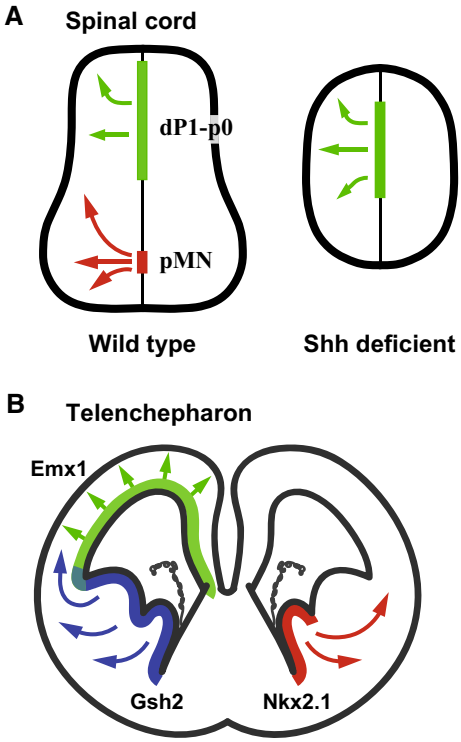

Fig. 4 Origins of cortical oligodendrocytes in the spinal cord (**a**) and brain (**b**). **a** There are at least two sources of OL-lineage cell generation in the embryonic spinal cord: the pMN domain and more dorsal region. Oligodendrogenesis from the pMN domain is dependent on Shh and disrupted in Shh-deficient mice, whereas dorsal oligodendrogenesis remains in such mice. **b** A revised model of oligodendrogenesis in the forebrain showing that three sequential waves of OPC generation from neural precursors in different regions: the $Nkx2.1^+$ medial ganglionic eminence (MGE) starting at E12.5, the $Gsh2^+$ lateral-to-caudal GE starting at E15.5, and the $Emx1^+$ cortical ventricular zone starting around birth

domain is critical for motoneuron production, and dephosphorylation of Olig2 alters its binding partners and induces OPC generation from the pMN domain [37]. This suggests that OL-lineage cells derived from the pMN domain are generated under strong influence from Shh and the subsequent action of Nkx6 and Olig2.

Interestingly, some OPCs appear in the dorsal portion of the spinal cord in Shh- or Nkx6.1/6.2-deficient embryos after E15 [30], suggesting the presence of an Shh-independent source for OPC production during later embryonic stages. This idea is also supported by data obtained from wild-type embryos in studies using the Cre/loxP system. For example, lineage tracing using Cre recombination under the control of the promoter for the *Dbx1* gene, a homeobox transcription factor expressed in the p0 and dP6 domains of the developing spinal cord, or the promoter for the *Gsh2* and *Msx3* genes, expressed in even more dorsal spinal cord, shows that OPCs are also derived from the dorsal region [38, 39]. These findings suggest that there are at least two sources of OL-lineage cell generation in the

embryonic spinal cord: one dependent and the other independent of Shh.

Traditional perspectives on oligodendrocyte generation—forebrain

The sequential appearance of OPCs, first in the ventral region under the influence of Shh, followed by their presence in the dorsal region independent of Shh, also occurs in the telencephalon. OPCs in the telencephalon first appear in the VZ/SVZ of the ventral region from the medial ganglionic eminence (MGE) to the anterior entopeduncular area (AEP) that is defined by the expression of the *Gbx2* homeobox gene [40], around E12 [41, 42]. The generation of OPCs in these regions is induced by Shh signaling, which was demonstrated by analyzing Nkx2.1-deficient mouse embryos [41]. Nkx2.1 is a homeodomain transcription factor and critical inducer of Shh in the telencephalon. Deletion of Nkx2.1 leads to the loss of Shh expression in cells surrounding the VZ from the MGE to the AEP, and OPC generation during early embryonic stages. Furthermore, in the Nkx2.1-deficient embryos, OPCs emerge and spread out from the GE to the cortex after E16, suggesting that Shh-independent OPCs also exist in the telencephalon [43]. Interestingly, analysis of mice deficient for *Mash1*, another bHLH transcription factor, indicated that Mash1 is required for the generation of the early population of OPCs in the ventral forebrain around E12, but not for the later population of OPCs [44]. Thus, two or more populations of OL-lineage cells may exist in the adult mammalian brain, one derived from the ventral forebrain under the influence of Shh and the other(s) from the dorsal forebrain independent of Shh activity.

Revised perspective on oligodendrocyte generation—forebrain

A lineage-tracing study using Cre-transgenic mice supports the above hypotheses and suggests three waves of OPC generation (Fig. 4b) [45]. The earliest wave originates from the ventral forebrain as indicated above in the traditional point of view, in which OPCs are derived from Nkx2.1-lineage cells of the MGE and AEP. MGE/AEP-derived OPCs migrate tangentially into the cortex where they mature and contribute to a subpopulation of myelinating OLs in the adult cortex [46]. Interestingly, most MGE/AEP-derived OLs in the cortex seem to be eliminated postnatally although they survive in the ventral portion of the adult brain [45]. The second wave of OPC generation starts from the lateral ganglionic eminence (LGE); these are labeled in *Gsh2*-Cre transgenic mice because *Gsh2* is expressed in the VZ/SVZ of the LGE and MGE in the developing brain. The third and final wave of OPCs are derived from the dorsal neural precursors which express *Emx1*, a dorsal forebrain specific homeobox gene, as shown by the analysis of *Emx1*-Cre mice. These results demonstrate that most, if not all, of the OLs in the adult cortex are derived from the $Emx1^{+}$ dorsal forebrain and $Gsh2^{+}$ LGE [45].

Our model of oligodendrocyte generation

We have reported that dorsal neural precursor cells never contribute to cortical OLs in the adult brain based on an in utero electroporation study using the Cre/loxP system [10, 46]. This appears to be inconsistent with a recent paper showing that *Emx1*-lineage OLs predominate in the adult cortex [45]. To resolve this apparent discrepancy, we performed a detailed examination of the origins of cortical OLs and found that neural precursor cells in the lateral dorsoventral boundary that express both *Emx1* and *Gsh2* are a source of adult cortical OLs, whereas those in the dorsal forebrain, excluding the boundary region, only produce neurons and astrocytes (Fig. 5a, b). Thus, the *Emx1*- and *Gsh2*-lineage OLs in the adult cortex shown by the preceding study [45] might originate from the *Emx1*/*Gsh2*-expressing boundary region. Surprisingly, neural precursor cells in the cortico-striatal (lateral) as well as cortico-septal (medial) boundary regions differentiate into cortical OLs, suggesting that both the lateral and medial dorsoventral boundary regions represent a specialized niche for the generation of cortical OLs (Fig. 6a) [10]. In contrast, OLs in the dorsal-most cortex were never labeled by in utero electroporation in our study, suggesting the possibility of yet another source of cortical OLs in addition to the lateral and medial boundary regions (Fig. 6b).

Roles for Wnt signaling in the generation of cortical OLs

Oligodendrogenesis is under the influence of several extrinsic factors, among which the Wnt family of proteins plays a major role in suppressing the generation of OPCs from neural precursors [47–49]. Given that Wnt signaling is activated in the dorsomedial portion of the forebrain, it is possible that dorsal neural precursor cells are suppressed by Wnts to differentiate into OL-lineage cells. Inhibition of Wnt signaling by electroporation of *Dkk*, an inhibitor of Wnt signals, or a constitutively active form of β-catenin, results in the generation of a substantial number of OLs from dorsal neural precursor cells (Fig. 5c) [10, 48]. Thus, dorsal neural precursor cells retain their oligodendrogenic capability but are inhibited by Wnts and other extrinsic factors.

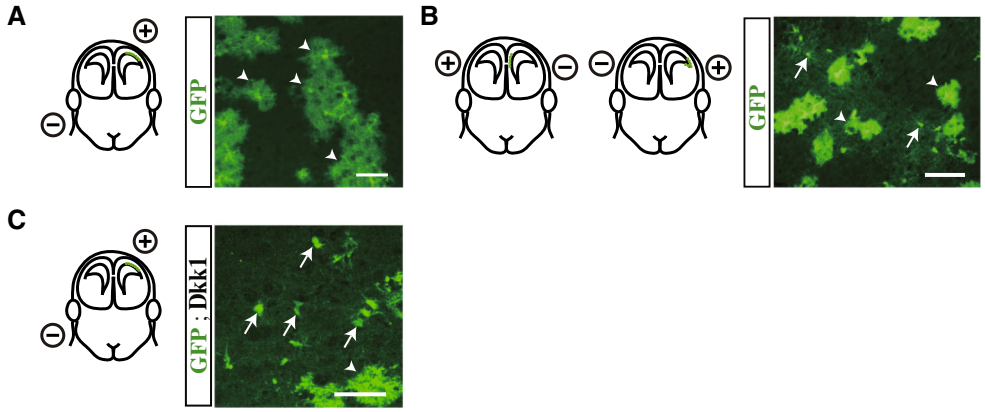

Fig. 5 In utero electroporation. Neural precursor cells in the dorsal cortex (**a**) or lateral and medial dorsoventral boundary (**b**) were labeled by electroporating E15.5 Z/EG reporter mouse embryos with a Cre recombinase expression plasmid. GFP^{+} cells were traced in coronal sections of P30 mouse brains and classified as oligodendrocytes (*arrows*), astrocytes (*arrowheads*), or neurons (not shown) based on morphology. **c** Suppression of Wnt signaling by the expression of *Dkk* caused neural precursor cells in the dorsal cortex to also differentiate into oligodendrocytes (*arrows*). *Scale bars* 50 μm (modified from Naruse et al. [10])

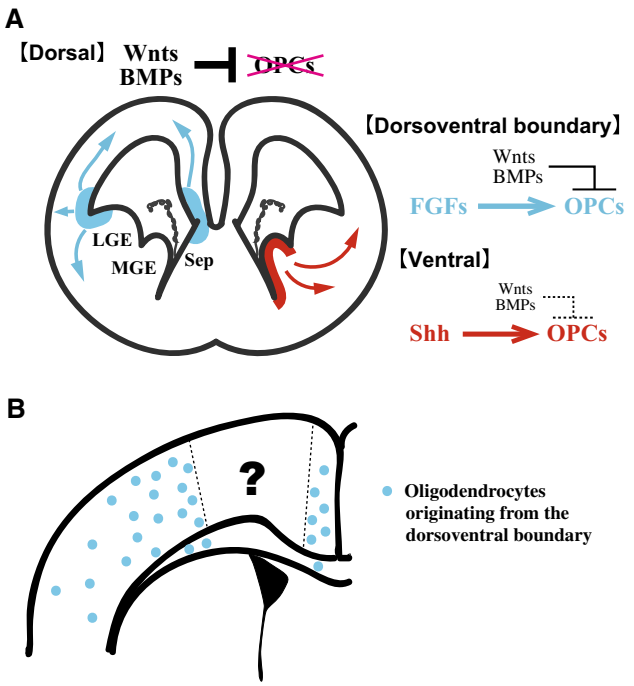

Fig. 6 Proposed model of cortical oligodendrogenesis. **a** Ventral oligodendrogenesis is dependent on Shh signaling. Shh-independent generation of oligodendrocyte precursor cells (OPCs) occurs at the lateral and medial dorsoventral boundary, where FGF signaling may overcome the suppression of oligodendrogenesis by Wnt signaling. **b** The origins of the dorsal-most portion of the adult cortex remain to be determined

Roles for FGF signaling in the generation of cortical OLs

Wnt proteins are secreted from the cortical hem in the developing brain and distributed in a gradient, with higher concentrations dorsomedially and lower concentrations ventrolaterally [52]. The strong oligodendrogenesis-suppressing Wnt signal that is active in the dorsomedial portion of the embryonic forebrain appears contradictory to our finding that cortical OLs are derived from the medial dorsoventral boundary region. One possible explanation is that Wnt signaling is inhibited by endogenous factor(s) in this region. However, this seems unlikely because *Axin2*, a downstream Wnt target, is expressed in the medial boundary region [10]. Alternatively, an oligodendrogenesis-inducing factor(s) may overcome this Wnt activity.

Proteins of the FGF family are also good candidates for potential oligodendrogenesis-inducing factors. FGF-2 has important effects on the proliferation, migration, and differentiation of OPCs, and also affects the morphology and function of mature OLs [50–52]. FGF-2 also stimulates the generation of OLs from cultured cortical neural precursors of both the embryonic spinal cord and cerebral cortex [53–56]. Consistent with these in vitro studies, microinjection of FGF-2 into the lateral ventricle of E13.5 mouse embryos increases the proliferation of neuroepithelial cells and the number of OPCs generated from the GE. In addition, ectopic generation of OPCs is observed in the dorsal cortex near the lateral and medial dorsoventral boundary [57], suggesting that FGF-2 overrides Wnt activity and induces the generation of OPCs from the medial dorsoventral boundary region (Fig. 6a). Further analysis of the interaction between Wnt and FGF signaling is needed to clarify these roles.

Perspectives

The cortico-striatal border has been shown to be a specialized region for the generation of cortical OLs in the adult mouse brain. This finding may contribute to future

investigation into unknown mechanisms responsible for constructing the mammalian brain. During the period of early embryogenesis, neural precursor cells at the lateral dorsoventral boundary migrate out to the primordium of the basal telencephalic limbic system [58]. These neural precursor cells seem to produce neurons of the piriform cortex and amygdala during earlier embryonic stages, then switch their fate to produce cortical OLs during later embryonic and postnatal stages, although the molecular mechanism for this fate switch remains unknown. Here, the question arises: what is the function of neural precursor cells at the medial dorsoventral boundary? Given that the lateral domain of the cortico-striatal border is involved in neurogenesis of the limbic system, it is reasonable to hypothesize that the contralateral side has a similar purpose. This is an intriguing possibility because development of the limbic system remains largely unexplained. Moreover, since limbic structures regulate many fundamental traits such as emotions, memory, and drives, elucidating their development may provide us with clues to a better scientific understanding and potential future cures of psychiatric disorders.

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